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Applicant REESE, Colin, Bernard et al	

1. The designated Office is hereby notified of its election made:

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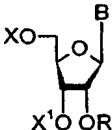
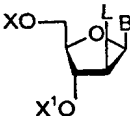
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(21) International Application Number: PCT/GB00/00965 (22) International Filing Date: 15 March 2000 (15.03.00) (30) Priority Data: 9906328.1 19 March 1999 (19.03.99) GB (71) Applicant (for all designated States except US): AVECIA LIMITED [GB/GB]; Hexagon House, Blackley, Manchester M9 8ZS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): REESE, Colin, Bernard [GB/GB]; King's College London, The Strand, London WC2R 2LS (GB). SONG, Quanlai [CN/US]; Apartment 300, 586 E. Barham Drive, San Marcos, CA 92078 (US). (74) Agents: REVELL, Christopher et al.; Avecia Limited, Intellectual Property Group, Hexagon House, P.O. Box 42, Blackley, Manchester M9 8ZS (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: 2'-SUBSTITUTED RNA PREPARATION <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(1)</p> </div> <div style="text-align: center;">  <p>(2)</p> </div> </div> (57) Abstract <p>A process for the preparation of a compound of formula (1) is provided, which comprises the reaction a compound of formula (2) with a compound of formula $Al(OR)_3$ wherein R is as defined above, under substantially anhydrous conditions. X, and X' are each independently H or a protecting group, B is a base; R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted, and L is a leaving group.</p>		

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2'-SUBSTITUTED RNA PREPARATION

The present invention relates to a process for preparing 2'-O-substituted nucleosides, and more particularly to a process for the preparation of 2'-O-substituted uridine and cytidine.

5 The possibility that synthetic oligonucleotides might be effective inhibitors of gene expression and be used as chemotherapeutic agents has stimulated much research work in recent years. In order to avoid their degradation by cellular nucleases, it is essential that such oligonucleotides should be modified. Modifications can be made to the internucleotide linkages, the base residues and the sugar residues. A large number of oligonucleotide analogues in which the internucleotide linkages have been modified, especially as phosphorothioates with non-bridging sulphur atoms, have been described. 10 Several of these phosphorothioate analogues are promising drug candidates that are now undergoing clinical trials. However, phosphorothioates do have some disadvantages. Thus, they do not display optimal RNA-binding properties and they also have a tendency to bind to proteins in a non-specific manner. Possible base modifications are clearly limited as they must not lead to a significant decrease in hybridisation properties. 15 Recently, considerable interest has been directed towards the modification of the sugar residues. One particular type of modification involves the introduction of 2'- α -alkoxy groups (as in 2'-O-alkyl-oligoribonucleotides). While, in general, small alkoxy groups (such as methoxy) promote better hybridisation properties with complementary ribonucleic acids (RNA), nuclease resistance tends to increase with an increase in the size of the alkoxy group. 2-Methoxyethoxy has emerged as an alkoxy group that confers both good hybridisation properties and high nuclease resistance. It therefore seems likely that 2'-O-(2-methoxyethyl)-ribonucleosides will be incorporated into a second generation of potential oligonucleotide chemotherapeutic agents. For this reason, the development of convenient methods for the preparation of 2'-O-(2-methoxyethyl)-ribonucleosides has become a matter of much importance. 25

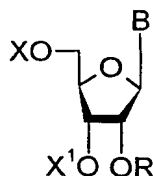
The preparation of 2'-O-(2-methoxyethyl)-ribonucleosides, starting from D-ribose, has previously been described. These preparations involved the use of protecting groups and required a relatively large number of steps. For example, 2'-O-(2-methoxyethyl)-5-methyluridine was prepared by Martin, P. *Helv. Chim. Acta* 1995, 78, 486-504 from D-ribose in 10 steps and in 33% overall yield. A later report by McGee and Zhai in Abstracts of American Chemical Society National Meeting, Division of Organic Chemistry, March 1996 paper 253 revealed a much more convenient procedure for the preparation of 2'-O-alkyl derivatives of the main pyrimidine ribonucleosides. Thus, when 5'-O-(4,4'-dimethoxytrityl)-2,2'-anhydro-1- β -D-arabinofuranosyluracil was heated with magnesium methoxide in N,N-dimethylformamide (DMF) at 100°C, 5'-O-(4,4'-dimethoxytrityl)-2'-O-methyluridine was obtained in 94% yield. Somewhat lower yields of the corresponding 5'- 35

O-ethyl-, 5'-O-(n-propyl)- and 5'-O-allyl-uridine derivatives were obtained in the reactions between the same substrate and the appropriate magnesium alkoxides. It was also reported that magnesium alkoxides could be replaced by calcium alkoxides.

Ross et al reported in *Nucleosides and Nucleotides*, 1997, 16, 1641-3 that when unprotected 2,2'-anhydro-1- β -D-arabinofuranosyluracil was heated with a twofold excess of trimethyl borate and a stoichiometric quantity of trimethyl orthoformate in methanol at 150°C, under pressure, for 42 h, 2'-O-methyluridine was obtained in 86% isolated yield. 2'-O-Methyl-5-methyluridine was similarly prepared from 2,2'-anhydro-5-methyl-(1- β -D-arabinofuranosyluracil) by the borate ester procedure and, although no experimental details were provided, the preparation of 2'-O-methylcytidine was also reported. The yield of 2'-O-alkyl-uridine was stated to decrease with increasing alcohol size.

It remains desirable to identify additional or alternative routes for the preparation of 2'-O-substituted nucleosides.

According to the present invention, there is provided a process for the preparation of a compound of formula (1):



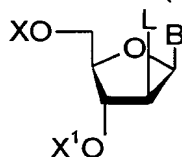
wherein:

X, and X' are each independently H or a protecting group;

B is a base; and

R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted;

which comprises reacting a compound of formula (2):



wherein

L is a leaving group; and

B, X and X' are as defined above

with a compound of formula $\text{Al}(\text{OR})_3$ wherein R is as defined above, under substantially anhydrous conditions.

When R is alkenyl, the alkenyl group is often a C_{1-4} alkenyl group, especially an allyl or crotyl group. When R represents alkyl, the alkyl group is preferably a C_{1-4} alkyl, and most preferably a methyl or ethyl group. When R represents alkoxyalkyl, the alkoxyalkyl group is often a C_{1-4} alkoxy C_{1-4} alkyl group, and preferably a methoxyethyl group. When R is alkynyl, the alkynyl group is often a C_{1-4} alkynyl group, especially a

propargyl group. The alkyl, alkenyl, alkynyl and alkoxyalkyl groups may themselves be substituted by one or more substituents, particularly halogen, especially F, Cl or Br, and amino substituents.

Examples of protecting groups which can be represented by X and X' include acid labile protecting groups, particularly trityl and substituted trityl groups such as dimethoxytrityl and 9-phenylxanthen-9-yl groups; acid-labile acetal protecting groups, particularly 1-(2-fluorophenyl)-4-methoxypiperidine-4-yl (Fmp); and base labile-protecting groups such as acyl groups, commonly comprising up to 16 carbon atoms, such as ethanoyl groups or fatty alkanoyl groups, including particularly linear or branched C₆₋₁₆ alkanoyl groups, such as lauroyl groups; benzoyl and substituted benzoyl groups, such as alkyl, commonly C₁₋₄ alkyl-, and halo, commonly chloro or fluoro, substituted benzoyl groups.

Other suitable protecting groups include those derived from gamma keto acids, such as levulinoyl groups and substituted levulinoyl groups. Substituted levulinoyl groups include 5-halo-levulinoyl, such as 5,5,5-trifluorolevulinoyl and benzoylpropionyl groups; and silyl and siloxane ethers, such as alkyl, commonly C₁₋₄ alkyl, and aryl, commonly phenyl, silyl ethers, particularly trialkylsilyl groups, often tri(C₁₋₄-alkyl)silyl groups, such as tertiary butyl dimethyl silyl and tertiary butyl diphenyl silyl groups.

Bases which can be represented by B include nucleobases, particularly purines, especially adenine (A) and guanine (G); and pyrimidines, especially thymine (T), cytosine (C), and uracil (U); and substituted derivatives thereof. Examples of substituents which may substitute the bases, in addition to protecting groups, include alkyl, especially C₁₋₄-alkyl, particularly methyl; halogen, particularly Cl or Br; amino; alkenyl, especially C₁₋₄-alkenyl and particularly allyl; alkoxyalkyl, especially C₁₋₄alkoxyC₁₋₄alkyl, particularly methoxyalkyl; and alkynyl, particularly propargyl, substituents. The alkyl, alkenyl, alkynyl and alkoxyalkyl groups may themselves be substituted by one or more substituents, particularly halogen, especially F, Cl or Br, and amino substituents.

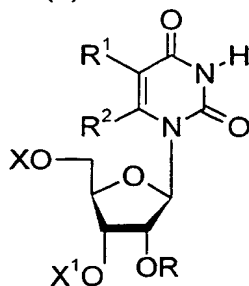
In addition to the presence of protecting groups X and X', bases employed in present invention may also be protected where necessary by suitable protecting groups. Protecting groups employed are those known in the art for protecting such bases. For example, A and/or C can be protected by benzoyl, including substituted benzoyl, for example alkyl- or alkoxy-, often C₁₋₄ alkyl- or C₁₋₄alkoxy-, benzoyl; pivaloyl; and amidine, particularly dialkylaminomethylene, preferably di(C₁₋₄-alkyl) aminomethylene such as dimethyl or dibutyl aminomethylene. G may be protected by a phenyl group, including substituted phenyl, for example 2,5-dichlorophenyl and also by an isobutyryl group. T and U generally are not protected, but in certain embodiments they may advantageously be protected, for example at O4 by a phenyl group, including substituted phenyl, for example 2,4-dimethylphenyl or at N3 by a pivaloyloxymethyl, benzoyl, alkyl or alkoxy substituted benzoyl, such as C₁₋₄ alkyl- or C₁₋₄ alkoxybenzoyl.

In certain embodiments, X and X' comprise a single protecting group which protects both the 3' and 5' positions. Examples of such groups include disiloxanes, especially tetraalkyldisiloxanes, such as tetraisopropyldisiloxane.

Leaving groups which can be represented by L include those leaving groups which can be displaced by a nucleophile of formula RO^- . Examples of preferred leaving groups include groups of formula $-OSO_2CH_3$, $-OSO_2CF_3$, Cl, Br, I, O-Mesyl, O-Brosyl and O-Tosyl groups.

In certain preferred embodiments, the leaving group comprises the base, B, chemically bonded to the 2'-position, commonly via an oxygen or sulphur atom or a group of formula $-NR^x$, wherein R^x is H or a C_{1-6} alkyl or aryl, such as a phenyl, group. Most preferably, the base is uracil bonded to the 2'-position via an oxygen atom.

Accordingly, a second aspect of the present invention provides a process for the preparation of a compound of formula (3):



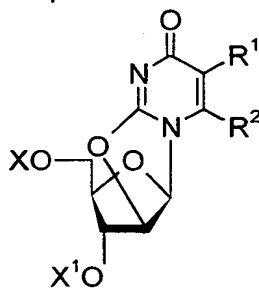
wherein:

X and X' are as defined above;

R^1 and R^2 are each independently H, alkyl, alkenyl, alkynyl, or halogen; and

R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted;

which comprises the reaction of a compound of formula (4)



wherein

X, X', R^1 and R^2 are as defined above;

with a compound of formula $Al(OR)_3$ wherein R is as defined above, under substantially anhydrous conditions.

When either of R^1 and R^2 is alkenyl, the alkenyl group is often a C_{1-4} alkenyl group, especially an allyl or crotyl group. When either of R^1 and R^2 represents alkyl, the alkyl group is preferably a C_{1-4} alkyl, and most preferably a methyl or ethyl group. When either

of R¹ and R² represents alkoxyalkyl, the alkoxyalkyl group is often a C₁₋₄ alkoxyC₁₋₄ alkyl group, and preferably a methoxyethyl group. When either of R¹ and R² is alkynyl, the alkynyl group is often a C₁₋₄ alkynyl group, especially a propargyl group. The alkyl, alkenyl and alkynyl groups represented by R¹ or R² may be substituted by one or more substituents, particularly halogen, especially F, Cl or Br, and amino substituents. When either of R¹ and R² is halogen the halogen is preferably Cl, Br or I. Most preferably, both of R¹ and R² represent H, or R¹ represents C₁₋₄ alkyl and R² represents H.

The process according to the present invention takes place in the presence of a suitable substantially anhydrous solvent. Examples of suitable solvents include halocarbons such as chloroform, 1,2-dichloroethane and chlorobenzene; esters, particularly alkyl esters such as ethyl acetate, and methyl or ethyl propionate; amides such as N-methylpyrrolidinone, dimethylformamide and particularly dimethylacetamide; lower alkyl, for example C₂₋₄ nitriles such as acetonitrile; ethers such as glyme and diglyme and cyclic ethers such as tetrahydrofuran and dioxane; tertiary amines, such as N-methylpyrrolidine and heterocyclic aromatic amines such as pyridine. and alcohols, most commonly the alcohol corresponding to the group R, for example methanol, ethanol, methoxyethanol, allyl alcohol or propargyl alcohol.

The process of the present invention is often carried out at a temperature of from room temperature, such as about 25°C, up to the reflux temperature of the solvent employed. Temperatures above the normal boiling point of the solvent employed can be employed if desired by carrying out the process under super-atmospheric pressure conditions, for example in a sealed reaction vessel. Commonly, the temperature is in the range of from 50 to 150°C.

The process commonly takes place over a period ranging from several hours, for example from 4 to 12 hours, to several days, for example from 1 to 2 days, depending on the reagents and reaction conditions employed.

When the compound of formula (1) comprises the base uracil, the uracil moiety may be converted to a cytosine moiety. Similarly, the uracil moiety comprised in the compound of formula (3) may also be converted to a cytosine moiety. The skilled man will recognise that a number of different techniques can be employed. Examples of such techniques include:

a) the nitrophenyl route (see Miah et al, Nucleosides and Nucleotides, 1997, 16, pp53-65) where for example the uracil containing compound is reacted with chlorotrimethylsilane in acetonitrile/1-methylpyrrolidine, then with trifluoroacetic anhydride, followed by 4-nitrophenol. The 4-nitrophenol moiety is then displaced with ammonia in aqueous dioxane to yield the cytosine-containing compound; and

b) the triazolation procedure, (see Divakar et al, J. Chem. Soc. Perkin Trans. 1, 1982, 1171-6) where for example the uracil containing compound is reacted with acetic anhydride in pyridine, then, after work up, with phosphoryl chloride, 1,2,4-triazole and

triethylamine in acetonitrile to give the 4-triazolopyrimidine. The triazole moiety is then displaced with ammonia in aqueous dioxane, and acetyl groups removed to yield the cytosine-containing compound.

Protecting groups can be removed using methods known in the art for the particular protecting group and function. For example, acyl protecting groups, such as ethanoyl and benzoyl groups, can be removed by treatment with a solution of ammonia in an alcohol such as ethanol.

Benzoyl, pivaloyl and amidine groups can be removed by treatment with concentrated aqueous ammonia.

Trityl groups present can be removed by treatment with acid, for example a solution of dichloroacetic acid in dichloromethane. With regard to the overall unblocking strategy an important consideration is that the removal of trityl, often DMTr, protecting groups ('detritylation') should proceed without concomitant depurination when base B represents a purine, especially adenine. Such depurination can be suppressed by effecting 'detritylation' with a dilute solution of hydrogen chloride at low temperature, particularly ca. 0.45 M hydrogen chloride in dioxane - dichloromethane (1:8 v/v) solution at -50°C. Under these reaction conditions, 'detritylation' can be completed rapidly, and in certain cases after 5 minutes or less.

Silyl protecting groups may be removed by fluoride treatment, for example with a solution of a tetraalkyl ammonium fluoride salt such as tetrabutyl ammonium fluoride.

Fmp protecting groups may be removed by acidic hydrolysis under mild conditions.

Compounds produced by the present invention may be incorporated in the assembly of a desired oligonucleotide by coupling with other nucleosides or oligonucleotides (which may themselves have been prepared using the present invention) and such a process forms a further aspect of the present invention. The coupling processes employed are those known in the art for the preparation of oligonucleotides.

The present invention is further illustrated, but not limited by, the following Examples.

General Experimental Details

Mps are uncorrected. ^1H and ^{13}C NMR spectra were measured at 360.1 and 90.6 MHz respectively, with a Bruker AM 360 spectrometer; tetramethylsilane was used as an internal standard. TLC was carried out with Merck silica gel 60 F₂₅₄ pre-coated plates (Art 5715), which were developed in solvent system A [CHCl_3 -MeOH (85:15 v/v)]. Short column chromatography was carried out on silica gel (Merck Art 7729). Acetonitrile and 1-methylpyrrolidine were dried by heating, under reflux, with calcium hydride and were then distilled. N,N-Dimethylacetamide (DMA) was dried by distillation over calcium hydride under reduced pressure. 2-Methoxyethanol was dried by heating with aluminium

foil (1g/250ml), under reflux, and was then distilled. Diethyl ether was dried over sodium wire.

Preparation of 2,2'-Anhydro-1- β -D-arabinofuranosyluracil

5 Uridine (12.21g, 50mmol), diphenyl carbonate (11.79g, 55mmol), sodium hydrogen carbonate (0.21g, 2.5mmol) and dry DMA (10ml) were heated together, with stirring, at 100°C. After 5h, the products were cooled to room temperature, and diethyl ether (100ml) was added with stirring. After 2 hours, the colourless precipitate (11.70g) was collected by filtration and was washed with ether (2 x 50ml). The sole nucleoside
10 constituent of the precipitated material was identified as 2,2'-anhydro-1- β -D-arabinofuranosyluracil (calculated quantitative yield, 11.31g) by comparison with authentic material.

Preparation of 2'-O-(2-Methoxyethyl)uridine

15 Aluminium foil (3.64g, 0.135 mol) and dry 2-methoxyethanol (135ml) were heated, under reflux, for ca. 1hr until all of the aluminium had been consumed. Crude (see above) 2,2'-anhydro-1- β -D-arabinofuranosyluracil (10.18g, ca. 43.5 mmol) was added and the reactants were heated, under reflux, for 48 hours. Absolute ethanol (200ml), followed by water (7.3ml, 0.405mol) and Celite were added to the cooled products. The resulting
20 mixture was heated, under reflux, for 10 minutes and was then filtered. The residue was washed with ethanol (3 x 100ml). The combined filtrate and washings were evaporated under reduced pressure to give a pale yellow solid. The material was purified by short column chromatography on silica gel (70g): the appropriate fractions, which were eluted with dichloromethane-methanol (90:10 v/v), were evaporated under reduced pressure to
25 give the title compound as a colourless solid (12.05g, ca. 91%).

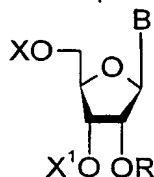
Preparation of 2'-O-(2-Methoxyethyl)cytidine

2'-O-(2-Methoxyethyl)uridine (6.05g, 20.0mmol), 1-methylpyrrolidine (20ml, 0.192mol), chlorotrimethylsilane (7.6ml, 59.9mmol) and dry acetonitrile (100ml) were
30 stirred together at room temperature. After 1 hour, the reactants were cooled to 0°C (ice-water bath) and trifluoroacetic anhydride (7.1ml, 50.3 mmol) was added dropwise over 5 minutes. After a further period of 30 minutes at 0°C, 4-nitrophenol (8.35g, 60mmol) was added to the stirred reactants which were maintained at 0°C. After 3 hours, the products were poured into saturated aqueous sodium hydrogencarbonate (200ml), and the
35 resulting mixture was extracted with dichloromethane (3 x 100ml). The combined organic layers were dried (MgSO₄), and evaporated under reduced pressure. Concentrated aqueous ammonia (d 0.88, 20ml) was added to a stirred solution of the residue in dioxane (100ml), contained in a sealed flask that was then heated at 55°C for 24 hours. The resulting yellow solution was concentrated under reduced pressure, and the residue was

evaporated with absolute ethanol (3 x 50ml). The products were fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane-methanol-triethylamine (93:7:0.5 to 90:10:0.5 v/v) were evaporated under the reduced pressure to give the title compound as an off-white solid (5.07g 84%).

CLAIMS

1. A process for the preparation of a compound of formula (1):



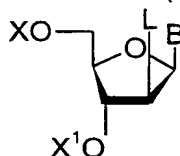
5 wherein:

X, and X' are each independently H or a protecting group;

B is a base; and

R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted;

10 which comprises reacting a compound of formula (2):



wherein

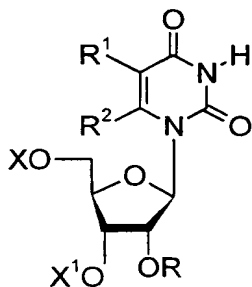
L is a leaving group; and

B, X and X' are as defined above

15 with a compound of formula $Al(OR)_3$ wherein R is as defined above, under substantially anhydrous conditions.

2. A process according to claim 1, wherein the leaving group is selected from the group consisting of $-OSO_2CH_3$, $-OSO_2CF_3$, Cl, Br, I, O-Mesyl, O-Brosyl, O-Tosyl and the base, B, chemically bonded to the 2'-position, via an oxygen or sulphur atom or a moiety of formula $-NR^x$, wherein R^x is H or a C_{1-6} alkyl or an aryl group.

3. A process for the preparation of a compound of formula (3):



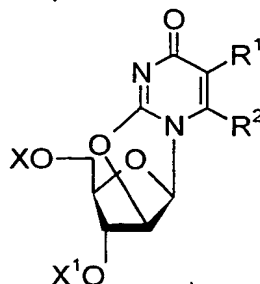
25 wherein:

X, and X' are each independently H or a protecting group;;

R¹ and R² are each independently H, alkyl, alkenyl, alkynyl, or halogen; and

R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted;

which comprises the reaction of a compound of formula (4)



wherein

X, X', R¹ and R² are as defined above;

with a compound of formula $\text{Al}(\text{OR})_3$ wherein R is as defined above, under substantially anhydrous conditions.

4. A process according to claim 3, wherein R¹ and R² are both H, or R¹ is C₁₋₄ alkyl, and R² is H.

5. A process according to any preceding claim, wherein R is a C₁₋₄ alkenyl group, a C₁₋₄ alkyl group, a C₁₋₄ alkoxyC₁₋₄ alkyl group or a C₁₋₄ alkynyl group.

6. A process according to claim 5, wherein R is a methoxyethyl group.

7. A process for the preparation of a compound of Formula (1) wherein B represents cytosine, or a substituted derivative thereof, which comprises:

- a) preparing a compound of Formula (1) wherein B represents uracil, or a substituted derivative thereof, by a process according to claim 1; and
- b) converting the uracil moiety to the equivalent cytosine moiety; or
- c) preparing a compound of Formula (3) by a process according to claim 2; and
- d) converting the uracil moiety therein to a cytosine moiety.

8. A process for the preparation of a product oligonucleotide which comprises the coupling to a nucleoside or an oligonucleotide of a compound prepared by a process according to any one preceding claim.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No

PCT/GB 00/00965

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/04 C07H19/06 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 27606 A (ISIS PHARMACEUTICALS INC ;COOK PHILLIP DAN (US); SANGHVI YOGESH S) 12 September 1996 (1996-09-12) page 33; claims 1-55	1
A	MC GEE D P C ET AL: "REACTION OF ANHYDRONUCLEOSIDES WITH MAGNESIUM ALKOXIDES: REGIOSPECIFIC SYNTHESIS OF 2'-O-ALKYLPYRIMIDINE NUCLEOSIDES" NUCLEOSIDES & NUCLEOTIDES, US, MARCEL DEKKER, INC, vol. 15, no. 11/12, 1 January 1996 (1996-01-01), pages 1797-1803, XP002066801 ISSN: 0732-8311 abstract	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 May 2000

Date of mailing of the international search report

23/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scott, J

INTERNATIONAL SEARCH REPORT

Int. .onal Application No

PCT/GB 00/00965

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>B.S.ROSS ET AL.: "A Novel and Economical Synthesis of 2'-O-Alkyl-Uridines." NUCLEOSIDES & NUCLEOTIDES., vol. 16, no. 7-9, 1997, pages 1641-1643, XP002137095 MARCEL DEKKER, INC., US ISSN: 0732-8311 the whole document</p> <p style="text-align: center;">-----</p>	1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 00/00965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9627606 A	12-09-1996	US 5760202 A	02-06-1998
		AU 5359496 A	23-09-1996
		CA 2214535 A	12-09-1996
		EP 0813539 A	29-12-1997
		JP 10512894 T	08-12-1998
		NO 974077 A	22-10-1997
		US 5861493 A	19-01-1999
<hr/>			

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) SMC 60344/WO

Box No. I TITLE OF INVENTION

2'-Substituted RNA Preparation

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Avecia Limited
Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

☐ This person is also inventor.

Telephone No.

0161 740 1460

Facsimile No.

0161 721 5801

Teleprinter No.

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☒

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

REESE, Colin Bernard
King's College London
the Strand
LONDON
WC2R 2LS
United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

REVELL, Christopher
Intellectual Property Group
Avecia Limited
PO Box 42, Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

Telephone No.

0161 721 1142

Facsimile No.

0161 721 5801

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SONG, Quanlai
586 E. Barham Drive, Apt. 300
San Marcos
CA 92078
USA

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
CN

State (that is, country) of residence:
US

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | |
| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> DZ Algeria |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available; in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication **"patent of addition,"** or **"certificate of addition,"** or if, in Box No. V, the name of the United States of America is accompanied by an indication **"continuation"** or **"continuation-in-part"**: in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box IV

FAWKES, David Melville
MAYALL, John
NELSON, Michael Andrew
PUGSLEY, Roger Graham
SCHMITT, Maja
SHELLER, Alan

All of Intellectual Property Group, Avecia Limited, PO Box 42, Hexagon House, Blackley, Manchester M9 8ZS, United Kingdom

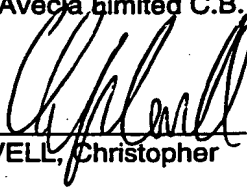
Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 19/03/1999 19 March 1999	9906328.1	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):	
ISA / EPO		Date (day/month/year)	Number Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING	
This international application contains the following number of sheets: request : 05 description (excluding sequence listing part) : 08 claims : 02 abstract : 01 drawings : 00 sequence listing part of description : 00 Total number of sheets : 16	This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT	
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).	
For Avecia limited C.B. Reese & Q. Song	
 REVELL, Christopher	

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SMC 60344/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/00965	International filing date (day/month/year) 15/03/2000	Priority date (day/month/year) 19/03/1999
International Patent Classification (IPC) or national classification and IPC C07H19/04		
Applicant AVECIA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 02/10/2000	Date of completion of this report 12.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vogt, T Telephone No. +49 89 2399 8477



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00965

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-8 as originally filed

Claims, No.:

3-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00965

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 3, 4 and claims 5 and 6 in relation to claim 3.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 3, 4, 5 (part), 6 (part)
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 3, 4, 5 (part), 6 (part)
Industrial applicability (IA)	Yes: Claims 3, 4, 5 (part), 6 (part)
	No: Claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/00965

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

IV Lack of unity of invention (Rule 13 PCT).

In reply to the previous raised objection for lack of unity between independent claims 1, 3, 7A, 7B and 8, the applicant indicated that he wishes to proceed with the subject matter relating to independent claim 3 as originally filed (claims 3, 4, and 5 and 6 partly).

V Reasoned statement (Rule 66(2) PCT).

Subject matter of the present application.

The present application proposes a process for the synthesis of 2'-O-substituted-nucleoside analogs.

Cited prior art documents. (Rule 64(1)PCT).

D1: WO-A-9627606.

D2: MCGEE D P C ET AL. (1996) NUCLEOSIDES & NUCLEOTIDES 15, 1797-1803.

D3: B.S.ROSS ET AL. (1997) NUCLEOSIDES & NUCLEOTIDES 16, 1641-1643.

D1 discloses a process for the synthesis of 2-O-substituted pyrimidines and oligomeric compounds therefrom. On p. 9, l. 35 D1 discloses the synthesis of compounds of formula 1 from the corresponding nucleotide via a reaction of the 2'-anhydro-pyrimidine analogue with $B(OR)_3$ in $R-OH$ similar to the process of the present application (compare examples 1, 20 and 41 of D1 with examples 1 and 2 of the present application). On p. 33, l. 11- 27 D1 discloses that the lewis acid trialkyl-boronate can be replaced by trialkyl-alumininate. D1 discloses a large variety of substituents for the 2'-position on p. 28, for instance methoxyethyl (examples 41, 42) and also modifications to 5-position of the base moiety (eg. 5-methyluridine, examples 20, 41, 42). D1 discloses that uridine analogues can be converted into cytosine analogues by known methods (p. 26, l. 22- p.27, l. 4). D1 further discloses that their compounds were incorporated into oligonucleotides (see Evaluation on p. 58 and further). The process of claim 3 of the present application appears to differ from that of claims 35-45 of D1 in that the Lewis acid was substituted by $Al(OR)_3$ instead of $B(OR)_3$ (cf. claim 39).

D2 discloses the synthesis of 2-O-alkyl-pyrimidine nucleosides using $Mg(OR)_3$ or $Ca(OR)_3$ from the 2'-anhydro-pyrimidine. D2 anticipates the use of its compounds in the synthesis of oligonucleotides (p. 1797, l. 7-16).

**INTERNATIONAL PRELIMINARY
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International application No. PCT/GB00/00965

D3 discloses a process similar to D1 and prepares 2-O-alkyl-Uridines using $B(OR)_3$ and the 2'-anhydro-analog. D3 also anticipates the use of their compounds in oligonucleotides (p. 1641, l. 5-10).

Novelty. (Art. 33(2) PCT).

The products obtained by the process of the present application are known from all three prior art documents.

The difference between the preparation process of the present application and the available prior art is the use of $Al(OR)_3$ instead of $B(OR)_3$ (D1 and D3) or $Mg(OR)_3$ and $Ca(OR)_3$ (D2).

The applicant argues in his reply (24.01.2001) that the generic disclosure of $Al(OR)_3$ over the broad term 'Lewis acid' involves the selection of two lists and therefore the requirement of novelty is met over said broad term used in claim 35 of D1. Indeed the examining authority agrees with this conclusion.

The subject matter of claims 3-6 meets the requirement of novelty. (Art. 33(2) PCT)

Inventive step. (Art. 33(3) PCT).

As discussed above and as exemplified by the comparison of the examples 1, 20 and 41 of D1 and examples 1 and 2 of the present application the only difference between said processes is the substitution of $B(OR)_3$ by $Al(OR)_3$.

The examining authority is of the opinion that for the determination of the presence of an inventive step one should not start the comparison between the process of the present application and D1 from the list of possible 'Lewis acids' disclosed therein, but from the generic disclosure $B(OR)_3$ (cf. claims 35 and 39, and examples 1, 20 and 41). From said generic disclosure the applicant made a selection from of only one list (p. 33, l. 17-22).

The problem solved by the applicant can therefore be seen as providing an alternative for $B(OR)_3$.

A person skilled in the art can deduce from D2 that not only $B(OR)_3$ but also $Mg(OR)_3$

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and Ca(OR)_3 give good results in the synthesis process as disclosed in claim 35 of D1. Since Mg and Ca are both listed as alternatives to Boron (see D1 p. 33, l. 20), a skilled artisan would consider the teaching of D2 as an incentive to test the other metals listed in the same sentence on p. 33 of D1 in order to obtain an alternative to B(OR)_3 .

Indeed the skilled artisan could not have anticipated the results in advance but he would have tested all other metals listed on p. 33 of D1. Hence, the substitution of B(OR)_3 by Al(OR)_3 was anticipated by D1 on p. 33, l. 11-27.

Furthermore, the applicant argues that higher yields are obtained with the process of the present application. However, the applicant must have overlooked procedure 3 of example 20 (p. 46, D1) where a yield of 100% is obtained with a purity of 97%.

As discussed above D1 discloses all further features found in dependent claims 4-6.

Based on the above the subject matter of claims 3-6 does not meet the requirement of inventive step. (Art. 33(3) PCT).

Industrial applicability. (Art. 33(4) PCT).

The products obtained by the processes of the present application find their application in the synthesis of oligonucleotides, which are useful for clinical applications. The subject matter of claims 3-6 meets the requirements of industrial applicability.

VII Defects in the description (Art. 5 PCT).

The applicant should identify the abbreviation 'Mps' used on p. 6, l. 32.

The applicant should identify D1-D3 in the description. (Rule 5.1 (II) PCT).

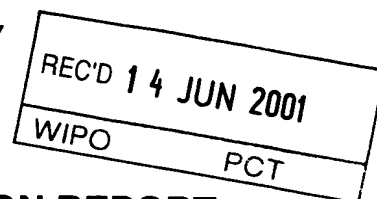
VIII Defects in the claims (Art. 6 PCT).

There appears to be an essential feature missing from claim 3. The reaction as described in said claims does not include the solvent R-OH. This feature is of importance because it is the nucleophile R-O^- from the solvent R-OH and not from the Lewis acid Al(OR)_3 which does the actual displacement, as evidenced by D1 (p. 11, l.

**INTERNATIONAL PRELIMINARY
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International application No. PCT/GB00/00965

19-24). In example 2 the applicant prepares the aluminate from the solvent as proposed by D1 (p. 12, l. 3-6) and thereby obtains a situation which again is proposed by D1 (p. 11, l. 27-28). The present application thereby obtains a mixture of Al(OR)_3 in ROH (similar to D1 in example 41) because a 10 fold excess of ROH was present in example 2. (Guidelines C-III, 4.4).



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



14

Applicant's or agent's file reference SMC 60344/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/00965	International filing date (day/month/year) 15/03/2000	Priority date (day/month/year) 19/03/1999
International Patent Classification (IPC) or national classification and IPC C07H19/04		
Applicant AVECIA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 02/10/2000	Date of completion of this report 12.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vogt, T Telephone No. +49 89 2399 8477 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00965

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-8 as originally filed

Claims, No.:

3-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00965

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 3, 4 and claims 5 and 6 in relation to claim 3.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 3, 4, 5 (part), 6 (part)
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 3, 4, 5 (part), 6 (part)
Industrial applicability (IA)	Yes: Claims 3, 4, 5 (part), 6 (part)
	No: Claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/00965

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
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International application No. PCT/GB00/00965

IV Lack of unity of invention (Rule 13 PCT).

In reply to the previous raised objection for lack of unity between independent claims 1, 3, 7A, 7B and 8, the applicant indicated that he wishes to proceed with the subject matter relating to independent claim 3 as originally filed (claims 3, 4, and 5 and 6 partly).

V Reasoned statement (Rule 66(2) PCT).

Subject matter of the present application.

The present application proposes a process for the synthesis of 2'-O-substituted-nucleoside analogs.

Cited prior art documents. (Rule 64(1)PCT).

D1: WO-A-9627606.

D2: MCGEE D P C ET AL. (1996) NUCLEOSIDES & NUCLEOTIDES 15, 1797-1803.

D3: B.S.ROSS ET AL. (1997) NUCLEOSIDES & NUCLEOTIDES 16, 1641-1643.

D1 discloses a process for the synthesis of 2-O-substituted pyrimidines and oligomeric compounds therefrom. On p. 9, l. 35 D1 discloses the synthesis of compounds of formula 1 from the corresponding nucleotide via a reaction of the 2'-anhydro-pyrimidine analogue with $B(OR)_3$ in $R-OH$ similar to the process of the present application (compare examples 1, 20 and 41 of D1 with examples 1 and 2 of the present application). On p. 33, l. 11- 27 D1 discloses that the lewis acid trialkyl-boronate can be replaced by trialkyl-alumininate. D1 discloses a large variety of substituents for the 2'-position on p. 28, for instance methoxyethyl (examples 41, 42) and also modifications to 5-position of the base moiety (eg. 5-methyluridine, examples 20, 41, 42). D1 discloses that uridine analogues can be converted into cytosine analogues by known methods (p. 26, l. 22- p.27, l. 4). D1 further discloses that their compounds were incorporated into oligonucleotides (see Evaluation on p. 58 and further). The process of claim 3 of the present application appears to differ from that of claims 35-45 of D1 in that the Lewis acid was substituted by $Al(OR)_3$ instead of $B(OR)_3$ (cf. claim 39).

D2 discloses the synthesis of 2-O-alkyl-pyrimidine nucleosides using $Mg(OR)_3$ or $Ca(OR)_3$ from the 2'-anhydro-pyrimidine. D2 anticipates the use of its compounds in the synthesis of oligonucleotides (p. 1797, l. 7-16).

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EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00965

D3 discloses a process similar to D1 and prepares 2-O-alkyl-Uridines using $B(OR)_3$ and the 2'-anhydro-analog. D3 also anticipates the use of their compounds in oligonucleotides (p. 1641, l. 5-10).

Novelty. (Art. 33(2) PCT).

The products obtained by the process of the present application are known from all three prior art documents.

The difference between the preparation process of the present application and the available prior art is the use of $Al(OR)_3$ instead of $B(OR)_3$ (D1 and D3) or $Mg(OR)_3$ and $Ca(OR)_3$ (D2).

The applicant argues in his reply (24.01.2001) that the generic disclosure of $Al(OR)_3$ over the broad term 'Lewis acid' involves the selection of two lists and therefore the requirement of novelty is met over said broad term used in claim 35 of D1. Indeed the examining authority agrees with this conclusion.

The subject matter of claims 3-6 meets the requirement of novelty. (Art. 33(2) PCT)

Inventive step. (Art. 33(3) PCT).

As discussed above and as exemplified by the comparison of the examples 1, 20 and 41 of D1 and examples 1 and 2 of the present application the only difference between said processes is the substitution of $B(OR)_3$ by $Al(OR)_3$.

The examining authority is of the opinion that for the determination of the presence of an inventive step one should not start the comparison between the process of the present application and D1 from the list of possible 'Lewis acids' disclosed therein, but from the generic disclosure $B(OR)_3$ (cf. claims 35 and 39, and examples 1, 20 and 41). From said generic disclosure the applicant made a selection from of only one list (p. 33, l. 17-22).

The problem solved by the applicant can therefore be seen as providing an alternative for $B(OR)_3$.

A person skilled in the art can deduce from D2 that not only $B(OR)_3$ but also $Mg(OR)_3$

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International application No. PCT/GB00/00965

and Ca(OR)_3 give good results in the synthesis process as disclosed in claim 35 of D1. Since Mg and Ca are both listed as alternatives to Boron (see D1 p. 33, l. 20), a skilled artisan would consider the teaching of D2 as an incentive to test the other metals listed in the same sentence on p. 33 of D1 in order to obtain an alternative to B(OR)_3 .

Indeed the skilled artisan could not have anticipated the results in advance but he would have tested all other metals listed on p. 33 of D1. Hence, the substitution of B(OR)_3 by Al(OR)_3 was anticipated by D1 on p. 33, l. 11-27.

Furthermore, the applicant argues that higher yields are obtained with the process of the present application. However, the applicant must have overlooked procedure 3 of example 20 (p. 46, D1) where a yield of 100% is obtained with a purity of 97%.

As discussed above D1 discloses all further features found in dependent claims 4-6.

Based on the above the subject matter of claims 3-6 does not meet the requirement of inventive step. (Art. 33(3) PCT).

Industrial applicability. (Art. 33(4) PCT).

The products obtained by the processes of the present application find their application in the synthesis of oligonucleotides, which are useful for clinical applications. The subject matter of claims 3-6 meets the requirements of industrial applicability.

VII Defects in the description (Art. 5 PCT).

The applicant should identify the abbreviation 'Mps' used on p. 6, l. 32.

The applicant should identify D1-D3 in the description. (Rule 5.1 (II) PCT).

VIII Defects in the claims (Art. 6 PCT).

There appears to be an essential feature missing from claim 3. The reaction as described in said claims does not include the solvent R-OH. This feature is of importance because it is the nucleophile R-O^- from the solvent R-OH and not from the Lewis acid Al(OR)_3 which does the actual displacement, as evidenced by D1 (p. 11, l.

**INTERNATIONAL PRELIMINARY
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International application No. PCT/GB00/00965

19-24). In example 2 the applicant prepares the aluminate from the solvent as proposed by D1 (p. 12, l. 3-6) and thereby obtains a situation which again is proposed by D1 (p. 11, l. 27-28). The present application thereby obtains a mixture of Al(OR)_3 in ROH (similar to D1 in example 41) because a 10 fold excess of ROH was present in example 2. (Guidelines C-III, 4.4).

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SMC 60344/WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 00965	International filing date (day/month/year) 15/03/2000	(Earliest) Priority Date (day/month/year) 19/03/1999
Applicant AVECIA LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00965

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/04 C07H19/06 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 27606 A (ISIS PHARMACEUTICALS INC ;COOK PHILLIP DAN (US); SANGHVI YOGESH S) 12 September 1996 (1996-09-12) page 33; claims 1-55	1
A	--- MCGEE D P C ET AL: "REACTION OF ANHYDRONUCLEOSIDES WITH MAGNESIUM ALKOXIDES: REGIOSPECIFIC SYNTHESIS OF 2'-O-ALKYLPYRIMIDINE NUCLEOSIDES" NUCLEOSIDES & NUCLEOTIDES,US,MARCEL DEKKER, INC, vol. 15, no. 11/12, 1 January 1996 (1996-01-01), pages 1797-1803, XP002066801 ISSN: 0732-8311 abstract --- -/--	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

8 May 2000

Date of mailing of the international search report

23/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Scott, J

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 00/00965

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>B.S.ROSS ET AL.: "A Novel and Economical Synthesis of 2'-O-Alkyl-Uridines." NUCLEOSIDES & NUCLEOTIDES., vol. 16, no. 7-9, 1997, pages 1641-1643, XP002137095 MARCEL DEKKER, INC., US ISSN: 0732-8311 the whole document -----</p>	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/00965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9627606 A	12-09-1996	US 5760202 A	02-06-1998
		AU 5359496 A	23-09-1996
		CA 2214535 A	12-09-1996
		EP 0813539 A	29-12-1997
		JP 10512894 T	08-12-1998
		NO 974077 A	22-10-1997
		US 5861493 A	19-01-1999
<hr/>			